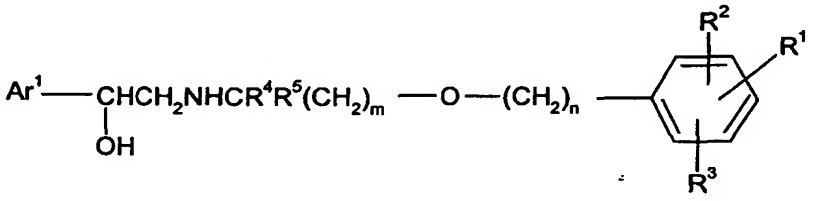
PHENYLETHANOLAMINE DERIVATIVES FOR THE TREATMENT OF RESPIRATORY DISEASES

The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2-adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine compounds including 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

Although salmeterol and the other commercially available β_2-adrenoreceptor agonists are effective bronchodilators, the duration of action is approximately 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2-adrenoreceptors and having an advantageous profile of action.

According to the present invention, there is provided a compound of formula (I)



(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;
n is an integer of from 3 to 11, preferably from 3 to 7;
with the proviso that m + n is 5 to 19, preferably from 5 to 12;

R^1 is $-XNR^6C(O)NR^7R^8$; wherein

X is selected from $-(CH_2)_p-$ and C_{2-6}alkenylene;

R^6 and R^8 are independently selected from hydrogen, C_{1-6}alkyl and C_{3-7} cycloalkyl; wherein said C_{1-6}alkyl and C_{3-7} cycloalkyl moieties may optionally be substituted by $-CO_2H$ or $-CO_2(C_{1-4})$alkyl;

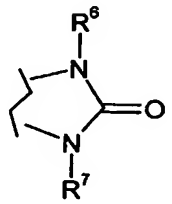
R^7 is selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $-C(O)R^9$, phenyl, naphthyl, hetaryl, and phenyl(C_{1-4}alkyl)- and R^7 is optionally substituted by 1 or 2 groups independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} alkoxy, $-NHC(O)(C_{1-6}$alkyl), $-SO_2(C_{1-6}$alkyl), $-SO_2$(phenyl), $-CO_2H$, and $-CO_2(C_{1-4}$alkyl) and $CONR^{10}R^{11}$;

R^9 is selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, $-CO_2H$, $CO_2(C_{1-4}$alkyl), phenyl, naphthyl, hetaryl, and phenyl(C_{1-4}alkyl)- and R^9 is optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} alkoxy, $-NHC(O)(C_{1-6}$alkyl), $-SO_2(C_{1-6}$alkyl), $-SO_2$(phenyl), $-CO_2H$, and $-CO_2(C_{1-4}$alkyl);

R^{10} and R^{11} each independently represent hydrogen, C_{1-4}alkyl or C_{3-7} cycloalkyl, and

p is an integer from 0 to 6, preferably from 0 to 4;

or R^1 is cyclised such that R^8 forms a bond with the phenyl ring to which R^1 is attached, via the ring carbon atom adjacent to R^1, so as to form a moiety of the formula:



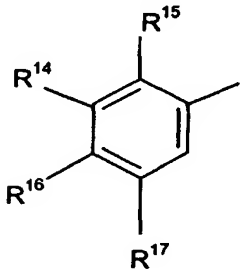
R^2 is selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, halo, and C_{1-6}haloalkyl;

R^3 is selected from hydrogen, hydroxy, C_{1-6}alkyl, halo, C_{1-6}alkoxy, phenyl, C_{1-6}haloalkyl, and $-SO_2NR^{12}R^{13}$;

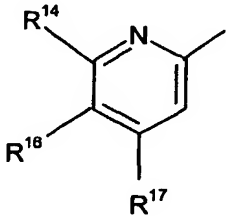
wherein R^{12} and R^{13} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, and phenyl (C_{1-4}alkyl), or R^{12} and R^{13} , together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;
and R^{12} and R^{13} are each optionally substituted by one or two groups selected from halo, C_{1-6}alkyl, and C_{1-6}haloalkyl;

R^4 and R^5 are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4;

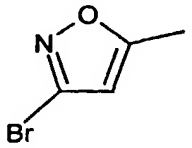
and Ar^1 is a group selected from



(a)

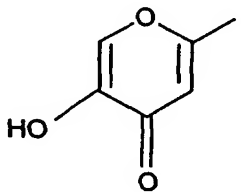


(b)



(c)

and



(d)

wherein R^{14} represents hydrogen, halogen, $-(CH_2)_qOR^{18}$, $-NR^{18}C(O)R^{19}$, $-NR^{18}SO_2R^{19}$, $-SO_2NR^{18}R^{19}$, $-NR^{18}R^{19}$, $-OC(O)R^{20}$ or $OC(O)NR^{18}R^{19}$,
and R^{15} represents hydrogen, halogen or C_{1-4} alkyl;

or R^{14} represents $-NHR^{21}$ and R^{15} and $-NHR^{21}$ together form a 5- or 6- membered heterocyclic ring;

R^{16} represents hydrogen, halogen, $-OR^{18}$ or $-NR^{18}R^{19}$;

R^{17} represents hydrogen, halogen, haloC_{1-4} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, $-OC(O)R^{20}$ or $OC(O)NR^{18}R^{19}$;

R^{18} and R^{19} each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^{18}R^{19}$, $-SO_2NR^{18}R^{19}$ and $-OC(O)NR^{18}R^{19}$, R^{18} and R^{19} independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

R^{20} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

q is zero or an integer from 1 to 4;

provided that in the group (a) when R^{14} represents $-(CH_2)_qOR^{18}$ and q is 1, R^{16} is not OH.

In a particular embodiment of this invention:
R^{14} represents hydrogen, halogen, $-NR^{18}C(O)R^{19}$, $-NR^{18}SO_2R^{19}$, $-SO_2NR^{18}R^{19}$, $-NR^{18}R^{19}$, $-OC(O)R^{20}$ or $OC(O)NR^{18}R^{19}$; and
R^{16} represents hydrogen, halogen, $-OR^{18}$ or $-NR^{18}R^{19}$.

In another embodiment of this invention:
R^{14} represents hydrogen, halogen, $-(CH_2)_qOR^{18}$, $-NR^{18}C(O)R^{19}$, $-NR^{18}SO_2R^{19}$, $-SO_2NR^{18}R^{19}$, $-NR^{18}R^{19}$, $-OC(O)R^{20}$ or $OC(O)NR^{18}R^{19}$; and
R^{16} represents hydrogen, halogen, or $-NR^{18}R^{19}$.

In another embodiment of this invention:
R^6 and R^8 are independently selected from hydrogen, C_{1-6}alkyl and C_{3-7} cycloalkyl;
R^7 is selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $-C(O)R^9$, phenyl, naphthyl, hetaryl, and phenyl(C_{1-4}alkyl)- and R^7 is optionally substituted by 1 or 2 groups independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} alkoxy, $-NHC(O)(C_{1-6}$alkyl), $-SO_2(C_{1-6}$alkyl), $-SO_2$(phenyl), $-CO_2H$, and $-CO_2(C_{1-4}$alkyl);
R^{14} is as defined above except that R^{14} does not represent hydrogen; and
all other substituents are as defined for formula (I).

In the definition of R^7, the term "hetaryl" means a 5- or 6-membered heteroaromatic ring, such as thienyl, pyrimidine, or pyridyl.

In the definition of R^{12} and R^{13} and in the definition of R^{18} and R^{19}, the term "5-, 6-, or 7-membered nitrogen containing ring" means a 5-, 6-, or 7- membered saturated or unsaturated ring which includes a nitrogen atom and optionally 1 or 2 other heteroatoms independently selected from nitrogen, sulphur, and oxygen. Suitable examples of such a ring include piperidinyl, morpholinyl, and piperazinyl.

In the definition of X, the term alkenylene includes both *cis* and *trans* structures. Suitably examples of alkenylene groups include –CH=CH-.

In the compounds of formula (I) R^1 is preferably as defined hereinafter.
R^2 is preferably hydrogen.
R^3 is preferably hydrogen or C_{1-6} alkyl.

In the compounds of formula (I), R^4 and R^5 are preferably independently selected from hydrogen and methyl, more preferably R^4 and R^5 are both hydrogen.

In the group R^1, the substituents R^6 and R^8 preferably each independently represent hydrogen.

R^7 is preferably selected from hydrogen, C_{1-6}alkyl; C_{1-6}alkyl substituted by a group selected from CO_2H, $CO_2(C_{1-4}$alkyl), $CONH_2$, and $CONH(C_{3-7}$cycloalkyl); phenyl; phenyl substituted by a group selected from halo, C_{1-6}alkyl, haloC_{1-6}alkyl and hydroxy; heteroaryl (eg. pyridyl or pyrimidinyl); C_{3-7}cycloalkyl; COPh and $COCO_2H$.

In the compounds of formula (I), m is suitably 3, 4 or 5, and preferably m is 5, and n is suitably 3 to 6 and preferably n is 3 or 4. More preferably n is 5 or 6 and n is 3 or 4 such that the sum of m + n is 8, 9 or 10, most preferably 9.

In the compounds of formula (I) the group Ar^1 is preferably selected from groups (a) and (b) above.

In said groups (a) and (b), when R^{14} represents halogen this is preferably chlorine or fluorine.

R^{18} and R^{19} preferably each independently represent hydrogen or methyl.

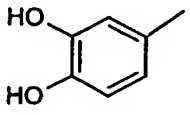
R^{20} preferably represents substituted phenyl.

The integer q preferably represents zero or 1.

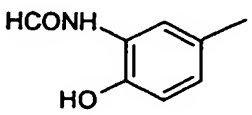
Thus for example $-(CH_2)_qOR^{18}$ preferably represents OH or $-CH_2OH$;
$NR^{18}C(O)R^{19}$ preferably represents $-NHC(O)H$;
$-SO_2NR^{18}R^{19}$ preferably represents $-SO_2NH_2$ or SO_2NHCH_3;
$-NR^{18}SO_2R^{19}$ preferably represents $NHSO_2CH_3$;
$NR^{18}R^{19}$ preferably represents $-NH_2$;
$-OC(O)R^{20}$ preferably represents substituted benzoyloxy eg. $OC(O)-C_6H_4-(p-CH_3)$; and
$-OC(O)N\ R^{18}\ R^{19}$ preferably represents $OC(O)N(CH_3)_2$.

When R^{14} represents NHR^{21} and together with R^{15} forms a 5- or 6- membered heterocyclic ring $-NHR^{21}-R^{15}-$ preferably represents a group:
$-NH-CO-R^{22}-$ where R^{22} is an alkyl, alkenyl or alkoxy group or moiety;
$-NH-SO_2R^{23}-$ where R^{23} is an alkoxy group or moiety;
$-NH-R^{24}-$ where R^{24} is an alkyl or alkenyl group or moiety optionally substituted by $COOR^{25}$ where R^{25} is C_{1-4} alkyl; or
-NH-CO-S-;
wherein said alkyl, alkenyl and alkoxy groups and moieties contain 1 or 2 carbon atoms.

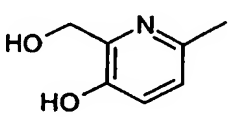
Particularly preferred groups (a) and (b) may be selected from the following groups (i) to (xxi):



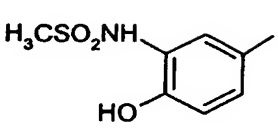
(i)



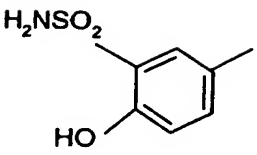
(ii)



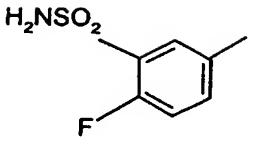
(iii)



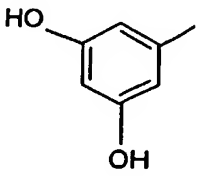
(iv)



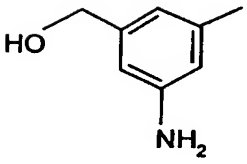
(v)



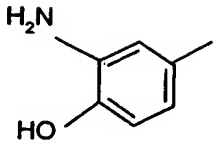
(vi)



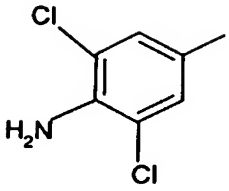
(vii)



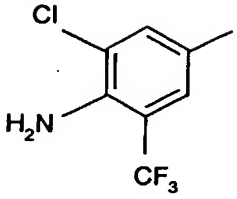
(viii)



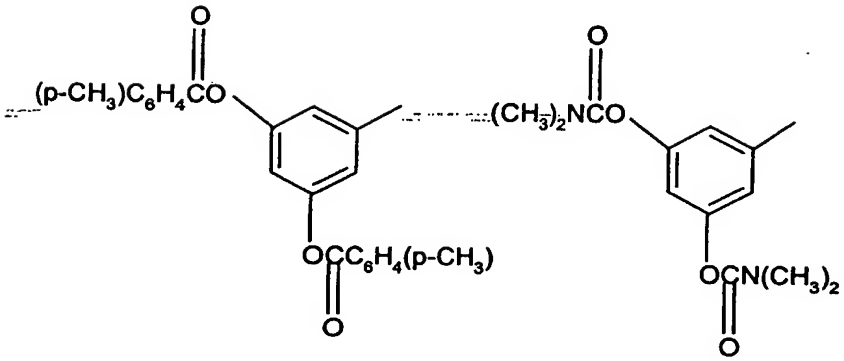
(ix)



(x)

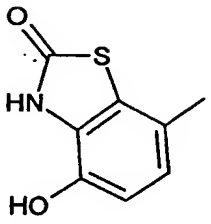


(xi)

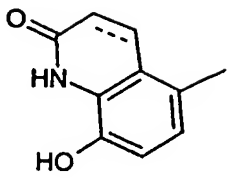


(xii)

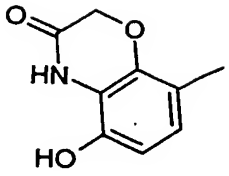
(xiii)



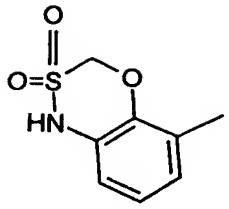
(xiv)



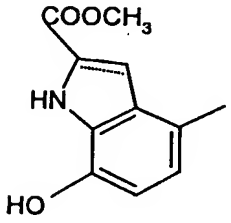
(xv)



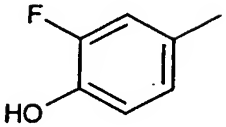
(xvi)



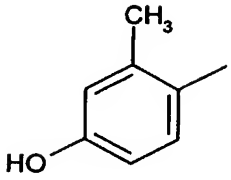
(xvii)



(xviii)



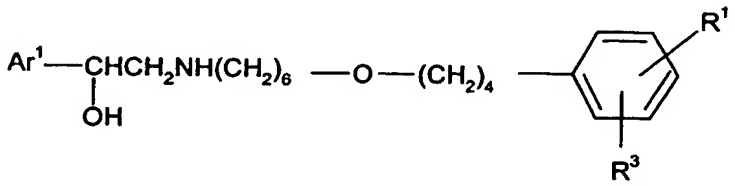
(xix)



(xx)

wherein the dotted line in (xv) and (xviii) denotes an optional double bond.

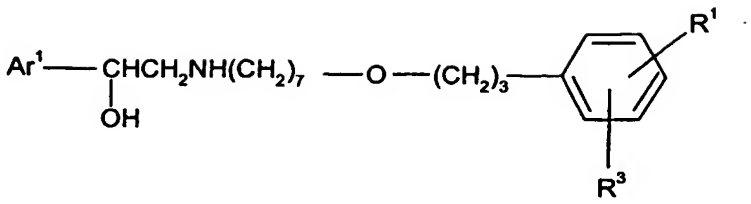
According to a preferred aspect of the invention, there is provided a compound of formula (Ia)



(Ia)

or a salt, solvate, or physiologically functional derivative thereof, wherein R^1 and R^3 are as defined above for formula (I).

According to a further preferred aspect of the invention, there is provided a compound of formula (Ib)



(Ib)

or a salt, solvate, or physiologically functional derivative thereof, wherein R^1 and R^3 are as defined above for formula (I).

In the compounds of formulae (I), (Ia) and (Ib), the group R^1 is preferably attached to the meta-position relative to the $-O-(CH_2)_n-$, $-O-(CH_2)_4-$ or $-O-(CH_2)_3-$ link respectively.

In the compounds of formulae (I), (Ia) and (Ib), the group R^1 is preferably $-(CH_2)p-NHC(O)NHR^7$ and R^7 is preferably hydrogen.

In the compounds of formulae (I), (Ia) and (Ib), p is preferably 0, 1, or 2.

In the compounds of formulae (I), (Ia) and (Ib), R^3 is preferably hydrogen or C_{1-6}alkyl, eg. methyl.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

The compounds of formulae (I), (Ia) and (Ib) include an asymmetric centre, namely the carbon atom of the

group. The present invention includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions.

Similarly, where R^4 and R^5 are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

Thus the compounds of formulae (I), (Ia) and (Ib) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

Preferred compounds of the invention include:

N-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]urea;
N-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]-*N'*-phenylurea;
N-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]-*N'*-pyridin-3-ylurea;
N-[3-(4-{[6-({2-hydroxy-2-[5-hydroxy-6-(hydroxymethyl)pyridin-2-yl]ethyl}amino)hexyl]oxy}butyl)-5-methylphenyl]urea.

and salts, solvates, and physiologically functional derivatives thereof.

Salts and solvates of compounds of formulae (I), (Ia) and (Ib) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formulae (I), (Ia) and (Ib) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I), (Ia) or (Ib) having the same physiological function as the free compound of formula (I), (Ia) or (Ib), for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulponic (for example p-toluenesulphonic, benzenesulphonic,

naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, methyl , methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

Pharmaceutically acceptable esters of the compounds of formulae (I), (Ia) and (Ib) may have a hydroxyl group converted to a C_{1-6}alkyl, aryl, aryl C_{1-6} alkyl, or amino acid ester.

As mentioned above, the compounds of formulae (I), (Ia) and (Ib) are selective β_2-adrenoreceptor agonists as demonstrated using functional or reporter gene readout from cell lines transfected with human beta-adrenoreceptors as described below. Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have shown an improved therapeutic index in animal models relative to existing long-acting β_2-agonist bronchodilators. As such, compounds of the invention may be suitable for once-daily administration.

Therefore, compounds of formulae (I), (Ia) and (Ib) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2-adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, including seasonal and allergic rhinitis).

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect the present invention provides such a method for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

In the alternative, there is also provided a compound of formula (I), (Ia) or (Ib) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated. In particular, there is provided a compound of formula (I), (Ia) or (Ib) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I), (Ia) or (Ib) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

The present invention also provides the use of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

In a further aspect, there is provided a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

The amount of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered by inhalation at a dose of from 0.0005mg to 10mg, preferably 0.005mg to 0.5mg for example 0.05mg to 0.5mg. The dose range for adult humans is generally from 0.0005mg to 10mg per day and preferably 0.01mg to 1mg per day, most preferably 0.05 to 0.5mg per day.

While it is possible for the compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I), (Ia) or (Ib) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the

methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations

generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di or poly-saccharides (eg. lactose or starch). Use of lactose is preferred.

Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134, US Patent Nos. 6,632,666, 5,860,419, 5,873,360 and 5,590,645 or Diskhaler, see GB 2178965, 2129691 and 2169265, US Patent No.s 4,778,054, 4,811,731, 5,035,237, the disclosures of which are hereby incorporated by reference) or metered in use (eg as in Turbuhaler, see EP 69715 or in the devices described in US Patents No. 6,321,747 the disclosures of which are hereby incorporated by reference). An example of a unit-dose device is Rotahaler (see GB 2064336 and US Patent No. 4,353,656, the disclosures of which are hereby incorporated by reference). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or

a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μm, preferably 2-5μm. Particles having a size above 20μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90μm and not less than 15% will have a MMD of less than 15μm.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Capsules and cartridges or for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insulator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose an acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example anti-inflammatory agents, anticholinergic agents (particularly an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example, an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic agent, another β_2-adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4-inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention

are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester and 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, more preferably 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2-adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Of particular interest is use of the compound of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and

the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

A method for determining IC_{50}s ratios is set out in US patent 5,998,428 which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/51599 for an another description of said assay.

The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity.

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC_{50} ratio of about 0.1 or greater; said ratio is the ratio of the IC_{50} value for competing with the binding of 1nM of [^{3}H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC_{50} value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[^{3}H]-cAMP as the substrate.

Most preferred are those PDE4 inhibitors which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC_{50} ratio of 0.1 or greater.

Other compounds of interest include:
Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-

(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomalast) and its salts, esters, pro-drugs or physical forms;

AWD-12-281 from Asta Medica (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vemalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther,1998, 284(1): 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M_1 and M_2 receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:

Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.

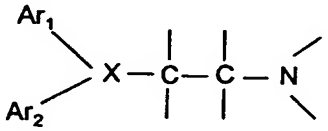
Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

Hyoscyamine (*d*, *l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt- CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperizine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperizine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: cholropheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a

combination as defined above together with a physiologically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

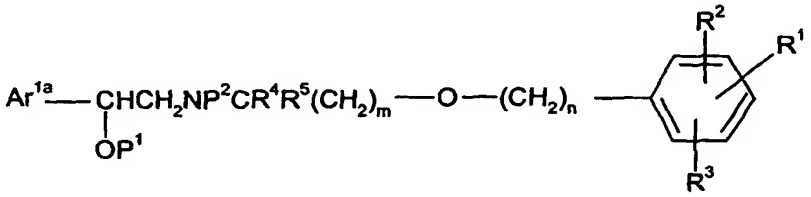
According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I), (Ia) or (Ib) or a salt, solvate, or physiologically functional derivative thereof which comprises a process (a) or (b) as defined below followed by the following steps in any order:

(i) optional removal of any protecting groups;

(ii) optional separation of an enantiomer from a mixture of enantiomers;

(iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

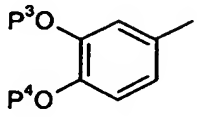
In one general process (a), a compound of formula (I), (Ia) or (Ib) may be obtained by deprotection of a protected intermediate, for example of formula (II):



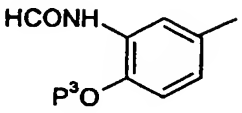
(II)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, m, and n are as defined for the compound of formula (I), (Ia) or (Ib), Ar^{1a} represents an optionally protected form of Ar^1; and P^1 and P^2 are each independently either hydrogen or a protecting group, provided that the compound of formula (II) contains at least one protecting group.

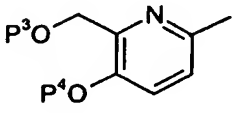
Protected forms of the preferred groups Ar^1 may be selected from:



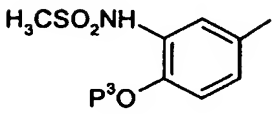
(ia)



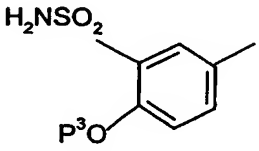
(iia)



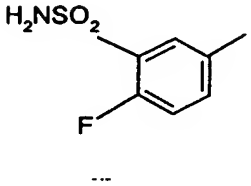
(iiia)



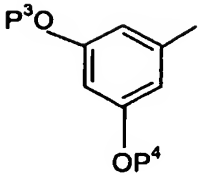
(iva)



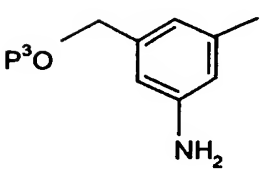
(va)



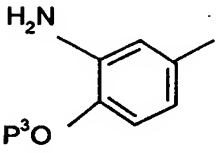
(via)



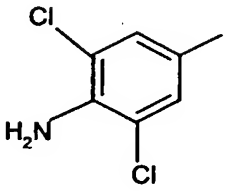
(viia)



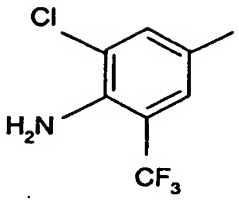
(viiia)



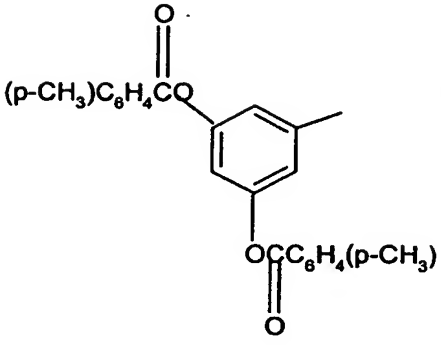
(ixa)



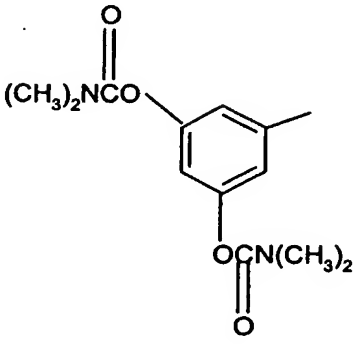
(xa)



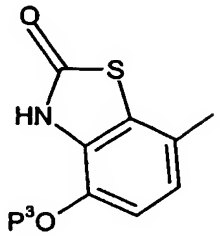
(xia)



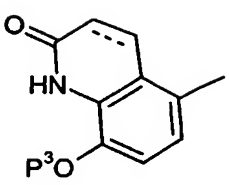
(xiia)



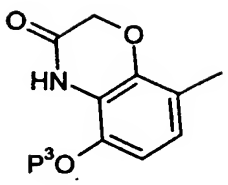
(xiiia)



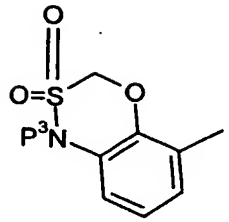
(xiva)



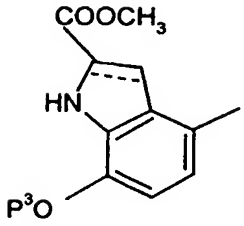
(xva)



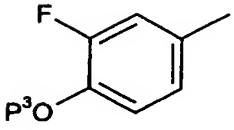
(xvia)



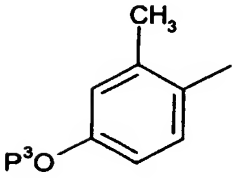
(xviia)



(xviiia)



(xixa)



(xxa)

wherein P^3 and P^4 are each independently either hydrogen or a protecting group provided that at least one of P^3 and P^4 is a protecting group, and the dotted line in (xva) and (xviiia) denotes an optional double bond. It will be appreciated that when Ar^1 represents a group (vi), (x), (xi), (xii) or (xiii) no protection is required.

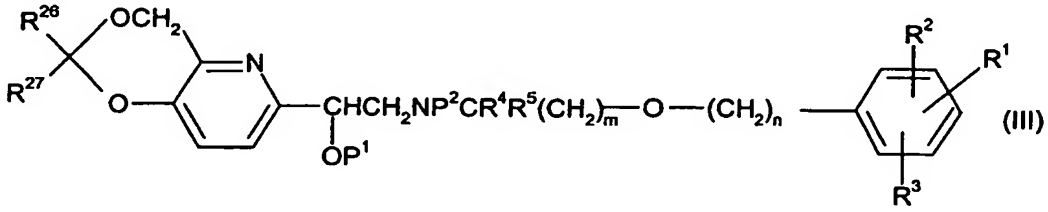
Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by P^3 and P^4 are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by P^2 include benzyl, α-methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective

functionalisation of a single amino or hydroxyl function. For example, the –CH(OH) group may be orthogonally protected as – $CH(OP^1)$ using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene and Peter G M Wuts (see above).

The deprotection to yield a compound of formula (I), (Ia) or (Ib) may be effected using conventional techniques. Thus, for example, when P^2, P^3, and/or P^4 is an aralkyl group, this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

When P^3 and/or P^4 is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by P^2 may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene and Peter G M Wuts (see above). In a particular embodiment of process (a), when Ar^1 is a group (iiia) P^3 and P^4 may together represent a protecting group as in the compound of formula (III):

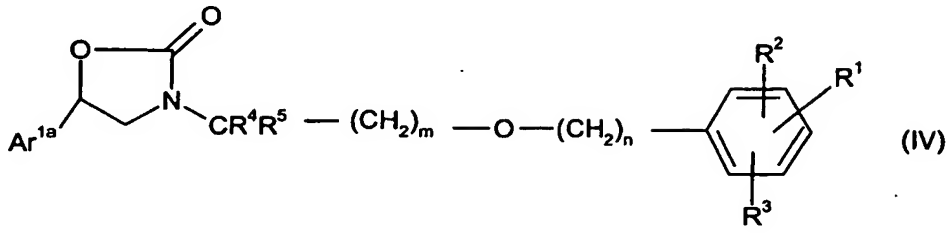


(III)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^{14}, P^1, P^2, m, and n are as defined for the compound of formula (I), (Ia) or (Ib), and R^{26} and R^{27} are independently selected from hydrogen, C_{1-6}alkyl, or aryl or R^{26} and R^{27} together form a C_{3-7} cycloalkyl ring. In a preferred aspect, both R^{26} and R^{27} are methyl, or R^{26} is hydrogoen and R^{27} is phenyl.

The compound of formula (III) may be converted to a compound of formula (I), (Ia) or (Ib) by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketalisation in an alcohol, for example ethanol, in the presence of a catalyst such as an acid (for example, toluenesulphonic acid or a sulphonic acid ion exchange column such as SCX-2) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

Compounds of formulae (II) and (III) wherein P^2 is hydrogen may be prepared from the corresponding compound of formula (IV):

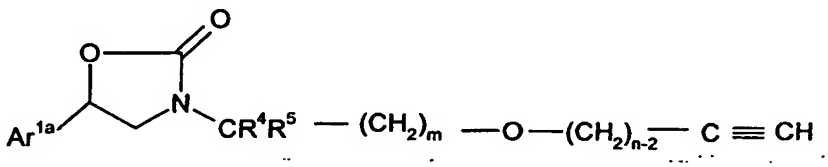


(IV)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, Ar^{1a} m, and n are as defined for the compound of formula (II) or (III).

The conversion of a compound of formula (IV) to a compound of formula (II) or (III) may be effected by treatment with a base, for example a non-aqueous base, such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran.

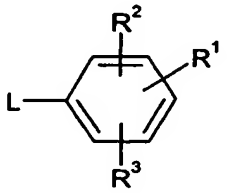
Compounds of formula (IV) may be prepared from the corresponding compound of formula (V):



(V)

or a salt or solvate thereof, wherein R^4, R^5, Ar^{1a}, m and n are as defined for the compound of formula (IV);

by coupling with a compound of formula (VI) or a precursor thereof:



(VI)

wherein R^1, R^2, and R^3 are as defined for the compound of formula (IV) and L is a leaving group, such as a halo group (typically, bromo or iodo) or a sulfonate ester such as a haloalkyl sulfonate (typically, trifluoromethanesulfonate).

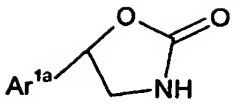
A suitable precursor of the compound of formula (VI) would be a compound of formula (VI) in which one or more of the substituents R^1, R^2, and R^3 is a group which is convertible to the desired group R^1, R^2, and/or R^3. For example, where R^1 is to be $-(CH_2)_pNR^6C(O)NR^7R^8$, a suitable precursor of the compound of formula (VI) would have the primary amine $-(CH_2)_pNH_2$ in place of the substituent R^1, such that the desired substituent R^1 may be formed by reaction with the appropriate isocyanate (i.e. R^7NCO) after the coupling with the compound of formula (V). Alternatively, R^1 is –XNCO (wherein X is as hereinbefore defined) which is coupled with an amine R^7NH_2 using standard procedures.

The coupling of compound of formula (V) with a compound of formula (VI) or a precursor thereof is conveniently effected in the presence of a catalyst system such as bis (triphenylphosphine) palladium dichloride and a copper catalyst such as cuprous iodide with an organic base such as a trialkylamine, for example, triethylamine or diisopropyl-ethylamine, in a suitable solvent, for example acetonitrile or dimethylformamide. The resulting alkyne may then be reduced, either with or without being isolated to form the compound of formula (IV). The reduction may be effected by any suitable method such as hydrogenation in the presence of a catalyst, for example, palladium/charcoal or platinum oxide.

Alternatively, after coupling of a compound of formula (V) to a compound of formula (VI), the resulting compound may be treated with a base, for example a non-aqueous base such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran, followed by reduction of the alkyne group to form a compound of formula (II) wherein P^2 denotes hydrogen.

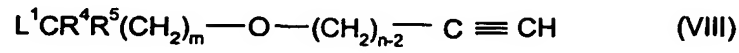
Compounds of formula (VI) are commercially available or may be prepared by methods well known to the person skilled in the art.

Compounds of formula (V) may be prepared by coupling a compound of formula (VII):



(VII)

or a salt or solvate thereof, wherein Ar^{1a} is defined for the compound of formula (V) with a compound of formula (VIII):



(VIII)

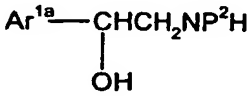
wherein R^4, R^5, m and n are as defined for the compound of formula (V) and L^1 is a leaving group, for example a halo group (typically bromo or iodo) or a sulfonate such as an alkyl sulfonate (typically, methanesulfonate), an arylsulfonate (typically, toluenesulfonate), or a haloalkyl sulfonate (typically, trifluoromethanesulfonate).

The coupling of a compound of formula (VII) with a compound of formula (VIII) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, or an inorganic base such as caesium carbonate, in an aprotic solvent, for example dimethylformamide.

Compounds of formula (VIII) may be prepared from the corresponding dihaloalkane and hydroxyalkyne by conventional chemistry, typically in the presence of an inorganic base, such as aqueous sodium hydroxide, under phase transfer conditions in the presence of an ammonium salt such as tetraalkylammonium bromide.

Compounds of formula (VII) may be prepared for example as desribed in WO02/066422.

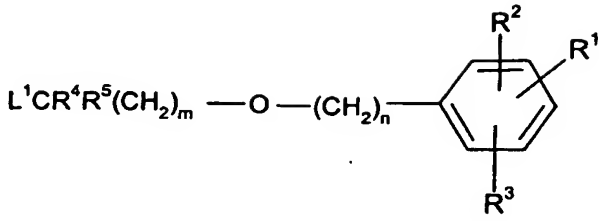
In a further process (b), a compound of formula (I), (Ia) or (Ib) may be obtained by alkylation of an amine of formula IX)



(IX)

wherein Ar^{1a} and P^2 are as hereinbefore defined;

with a compound of formula (X):



(X)

wherein R^1, R^2, R^3, R^4, R^5, m, and n are as defined for the compound of formula (I), (Ia) or (Ib) and L^1 is a leaving group such as halo (typically bromo); followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II).

The reaction of compounds of formulae (IX) and (X) is optionally effected in the presence of an organic base such as a trialkylamine, for example, diisopropylethylamine, and in a suitable solvent for example dimethyl formamide.

Compounds of formula (IX) are known in the art (for example EP-A 0947498) or may be readily prepared by a person skilled in the art.

Further details concerning preparation of compounds (IX) wherein Ar^{1a} is a group (iv) can be found in DE3524990; concerning the preparation of compounds (IX) wherein Ar^{1a} is a group (i), (vii), and (xv) in EP-A-162576; concerning the preparation of compounds (IX) wherein Ar^{1a} is a group (iii) in EP-A-220054; concerning the preparation of compounds (IX) wherein Ar^{1a} is a group (x) in GB2165542 and concerning the preparation of compounds (IX) wherein Ar^{1a} is a group (c) in GB2230523.

Compounds of formula (X) may be prepared by coupling a compound of formula (VI) as defined above, or a precursor thereof (wherein one or more of the substituents R^1, R^2 or R^3 is a group which is convertible to the desired group R^1, R^2, or R^3) with a compound of formula (VIII) as shown above wherein R^4, R^5, m, and n are as defined for the compound of formula (X) and L^1 is a leaving group as defined above.

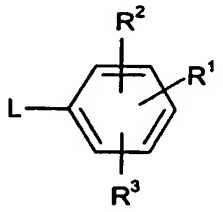
Suitable precursors of the compounds of formula (VI) for this purpose may be designed using the same principles as described above in relation to the coupling of a compound of formula (VI) with a compound of formula (V).

The coupling of a compound of formula (VIII) with a compound (VI) may be effected by methods analogous to those described above for coupling a compound of formula (V) with a compound of formula (VI), followed by reduction of the resulting alkyne, also as described above. If necessary, the substituents R^1, R^2, and/or R^3 may be formed by conventional conversions where a precursor is present.

Alternatively, a compound of formula (X) may be prepared by reacting an olefin of formula (XI):

$$L^1CR^4R^5(CH_2)_m\text{-}O\text{-}(CH_2)_{n-2}CH{=}CH_2 \qquad \text{(XI)}$$

wherein L^1, R^4, R^5, m and n are as defined for formula (VIII),
with a compound of formula (VI):



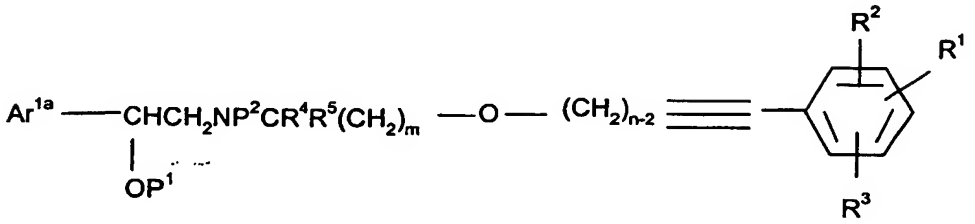
(VI)

as hereinbefore defined.

In this method, a compound of formula (XI) is initially reacted with a sterically hindered borane compound eg. a cyclic borane derivative such as 9-borabicyclo[3.3.1]nonane, thexylborane, catecholborane or disiamylborane, and followed by coupling with the compound (VI) in the presence of a catalyst such as palladium acetate, $PdCl_2$, $Pd(PPh_3)_4$, or $Pd_2(dba)_3$; and a phosphine such as triphenylphosphine, (di-tert-butylphosphino)biphenyl, tricyclohexylphosphine, triisopropylphosphine, tricyclopentylphosphine, or tri-tert-butylphosphine; and a base such as aqueous potassium or sodium phosphate, potassium or sodium carbonate, or sodium acetate.

Compounds of formula (XI) may be prepared by standard methods well known to those skilled in the art, for example in similar manner to the preparation of compounds of formula (VIII) described hereinabove.

In a yet further process (c) a compound of formula (I), (Ia) or (Ib) may be obtained by reduction of a compound of formula (XII):



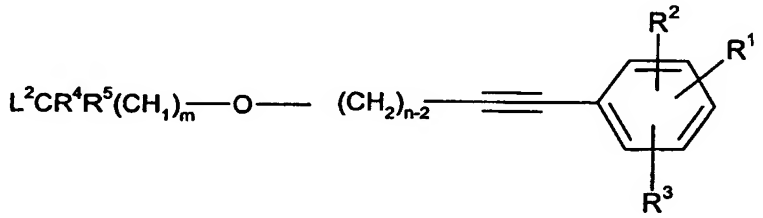
(XII)

wherein R^1, R^2, R^3, R^4, R^5, m and n are as defined for formula (I) and Ar^{1a}, P^1, and P^2 are are defined for formula (II).

The reduction may be effected by any suitable method such as hydrogenation in the presence of a catalyst, for example, palladium hydroxide, palladium/charcoal or a mixture thereof or platinum oxide. Suitably the reaction is effected at atmospheric pressure or more preferably at elevated pressure, to effect removal of P^2.

It will be appreciated that where Ar^{1a} represents Ar^1, and P^1 and P^2 each represent hydrogen, the reduction will yield a compound of formula (I), but where one or more of Ar^{1a}, P^2 and P^2 represents or contains a protecting group then reduction will yield a compound of formula (II) or (III), which may then be deprotected to give a compound of formula (I).

A compound of formula (XII) may be prepared by reacting a compound of formula (IX) as herein before defined with a compound of formula (XIII):



(XIII)

wherein R^1, R^2, R^3, R^4, R^5, m, and n are as defined for the compound of formula (I), (Ia) or (Ib) and L^2 is as defined for L and L^1 above.

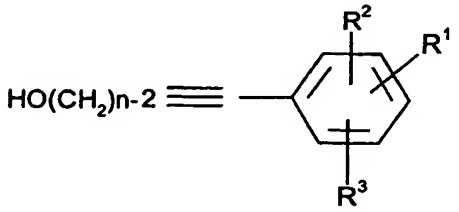
The reaction of a compound of formula (IX) with a compound of formula (XIII) is optionally effected in the presence of an organic base such as a trialkylamine, for example, diisopropylethylamine, and in a suitable solvent for example N,N-dimethylformamide.

A compound of formula (XIII) may be prepared by coupling a compound of formula (VI) as defined above with a compound of formula (VIII) as defined above, as described for the first stage of the preparation of compounds (X), without the reduction step.

An alkyne of formula (XIII) may also be prepared by reacting a compound of formula (XIV):

$$L^2CR^4R^5(CH_2)m\ L^3 \qquad (XIV)$$

wherein R^4, R^5 and n are as defined hereinabove and L^2 and L^3 each represent a leaving group, which groups may independently be selected for example from those defined above for L and L^1, with a compound of formula (XV):



(XV)

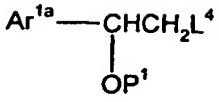
using conventional methods, for example as described for the preparation of compounds (VIII).

A compound of formula (XV) may be prepared by reacting a hydroxyalkyne

$$HO(CH_2)n\text{-}2 \equiv$$

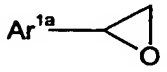
with a compound of formula (VI) using methods analogous to those described above for coupling a compound (V) with a compound (VI).

In a further process (d) a compound of formula (I), (Ia) or (Ib) may be prepared by reacting a compound of formula (XVI):



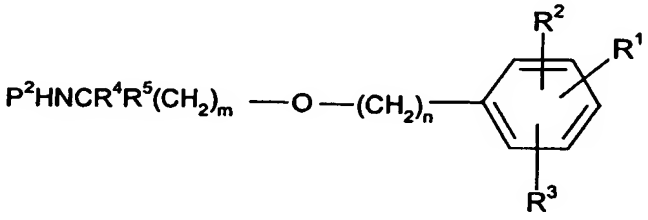
(XVI)

wherein Ar^{1a} and P^1 are as hereinbefore defined and L^4 is a leaving group as defined above for groups $L\text{-}L^3$ or a compound of formula (XVII):



(XVII)

wherein Ar^{1a} is as hereinbefore defined, with an amine of formula (XVIII):



(XVIII)

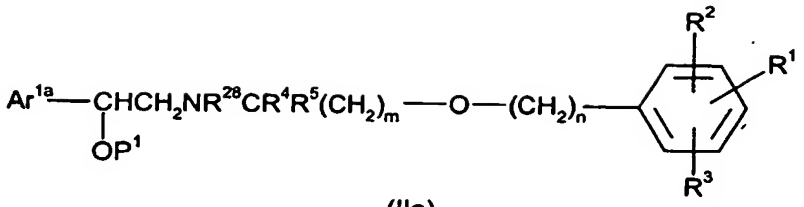
followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II).

The reaction may be effected using conventional conditions for such displacement reactions.

Compounds of formula (XVI) and (XVII) may be prepared by methods known in the art.

Compounds of formula (XVIII) may be prepared by reacting a compound of formula (X) with an amine P^2NH_2.

In a further process (e) a compound of formula (I), (Ia) or (Ib) may be prepared by removal of a chiral auxiliary from a compound of formula (IIa):



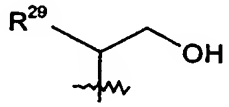
(IIa)

wherein R^1 – R^5, m and n are as defined for formula (I), Ar^{1a} and P^1 are as defined for formula (II) and R^{28} represents a chiral auxiliary.

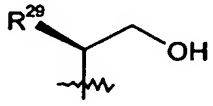
A "chiral auxiliary" is a moiety that is introduced into a molecule to influence the stereochemistry of the product formed, and is removed in whole or part at a later time. A chiral auxiliary may simultaneously function as a protecting group.

Many chiral auxiliaries are commercially available, and persons skilled in the art would choose one based on the properties desired i.e. the absolute stereochemistry desired and compatibility with the processes being used. Chiral auxiliaries suitable for use in this process include but are not limited to the S-isomer and/or the R-isomer of phenyl glycinol and substituted derivatives thereof.

The chiral auxiliary is preferably a moiety of the formula:



or a single enantiomer thereof, preferably



wherein R^{29} represents C_{1-6}alkyl or optionally substituted phenyl or benzyl wherein the optional substitution is one or more independently selected from C_{1-6}alkyl, halogen, hydroxy, C_{1-6}alkoxy or nitro e.g. para-hydroxyphenyl.

Preferably R^{29} represents phenyl optionally substituted as described above. Most preferably R^{29} represents unsubstituted phenyl.

The chiral auxiliary in this process may typically be removed by hydrogenolysis using for example a palladium on carbon catalyst or preferably using palladium hydroxide (Pearlman's catalyst). Advantageously when Pearlman's catalyst is used the removal of the chiral auxiliary is most efficient. This method of removal is especially suitable where R^{28} is phenyl or a substituted phenyl. Alternatively the nitrogen, to which the auxiliary is attached, may be derivatised under oxidising conditions to form the N-oxide before elimination by heating to give a secondary amine.

A compound of formula (IIa) may be prepared by methods analogous to those described above, for example in process (c).

A detailed description of a process analogous to Route (e) may be found in published International Application Number WO/0196278.

It will be appreciated that in any of the routes (a) to (e) described above, the precise order of the synthetic steps by which the various groups and moieties are introduced into the molecule may be varied. It will be within the skill of the practitioner in the art to ensure that groups or moieties introduced at one stage of the process will not be affected by subsequent transformations and reactions, and to select the order of synthetic steps accordingly.

The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating suitable diastereoisomers, or (ii) by direct synthesis from the appropriate chiral intermediates by the methods described above.

Optional conversions of a compound of formula (I), (Ia) or (Ib) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I), (Ia) or (Ib) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

According to a further aspect, the present invention provides novel intermediates for the preparation of compounds of formula (I), (Ia) or (Ib), for example:
compounds of formula (II) and (III) as defined above, or an optical isomer, a salt, or a protected derivative thereof.

For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

Throughout the examples, the following abbreviations are used:
LCMS: Liquid Chromatography Mass Spectrometry
MS mass spectrum
TSP+ve thermospray mass spectrum positive mode
RT : retention time
THF : tetrahydofuran
DMF : N,N-dimethylformamide
EtOAc ethyl acetate
EtOH ethanol
MeOH methanol
bp : boiling point
ca : circa
h : hour(s)
min : minute(s)
All temperatures are given in degrees centigrade.
Silica gel refers to Merck silica gel 60 Art number 7734.
Flash silica gel refers to Merck silica gel 60 Art number 9385.
Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module.
Bond Elut are prepacked cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian.
SCX-2 is a solid phase extraction column pre-packed with benzene sulfonic acid resin available from International Sorbent Technology.

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO_2H

5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5 min 0%B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Preparative mass directed HPLC was conducted on a Waters FractionLynx system comprising of a Waters 600 pump with extended pump heads, Waters 2700 autosampler, Waters 996 diode array and Gilson 202 fraction collector on a 10 cm X 2.54 cm ID ABZ+ column, eluting with 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B), using the following elution gradient: 0.0-1.0 min 15%B, 1.0-10.0 min 55%B, 10.0-14.5 min 99%B, 14.5-14.9 min 99%B, 14.9-15.0 min 15%B at a flow rate of 20 ml/min and detecting at 200-320 nm at room temperature. Mass spectra were recorded on Micromass ZMD mass spectrometer using electrospray positive and negative mode, alternate scans. The software used was *MassLynx 3.5* with *OpenLynx* and *FractionLynx* options.

Example 1

N-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]urea

i) *N*-[3-(4-{[6-(Benzyl{(2*R*)-2-[4-(benzyloxy)-3-(formylamino)phenyl]-2-hydroxyethyl}amino)hexyl]oxy}but-1-ynyl)phenyl]urea

A solution of 5-((1*R*)-2-{benzyl[6-(but-3-ynyloxy)hexyl]amino}-1-hydroxyethyl)-2-(benzyloxy)phenylformamide (WO 0276933) (0.67 g) and 3-iodophenylurea (0.41 g) in acetonitrile (5 ml) and triethylamine (2.2 ml) was treated with bis(triphenylphosphine) palladium dichloride (109 mg) and copper (I) iodide (54 mg) and the mixture was stirred under nitrogen for 4.5 h. The solvents were removed under reduced pressure and the residue was chromatographed on a Bond Elut silica cartridge (10 g) eluting with ethyl acetate-cyclohexane (1:4) to neat ethyl acetate and then on a Biotage cartridge (12 g) eluting with neat ethyl acetate to give *the title compound* (239 mg) LCMS RT = 2.69 min.

ii) *N*-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]urea

A solution of *N*-[3-(4-{[6-(benzyl{(2*R*)-2-[4-(benzyloxy)-3-(formylamino)phenyl]-2-hydroxyethyl}amino)hexyl]oxy}but-1-ynyl)phenyl]urea (232 mg) was hydrogenated over

10% palladium on carbon (35 mg) and palladium hydroxide (35 mg) in ethanol (10 ml) at a pressure of 100 psi overnight. The catalysts were removed by filtration and washed with ethanol. The combined filtrate and washings were evaporated under reduced pressure and the residue was purified by mass directed HPLC to give the title compound as the trifluoroacetate salt. The free base was obtained by ion exchange chromatography on an SCX-2 cartridge (10 g) eluting first with methanol and then with 2% aqueous ammonia in methanol to give *the title compound* (77.7 mg). LCMS RT = 2.18 min, ES+ve *m/z* 487 $(MH)^+$.

Example 2

N-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]-*N'*-phenylurea

i) N-[3-(4-{[6-(benzyl{(2*R*)-2-[4-(benzyloxy)-3-(formylamino)phenyl]-2-hydroxyethyl}amino)hexyl]oxy}but-1-ynyl)phenyl]-*N'*-phenylurea

Prepared using methods similar to those described in Example 1 i)

LCMS RT = 2.93 min.

ii) *N*-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]-*N'*-phenylurea

Prepared using methods similar to those described in Example 1 ii)

LCMS RT = 2.59 min, ES+ve *m/z* 563 $(MH)^+$

Example 3

N-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]-*N'*-pyridin-3-ylurea with (2*E*)-but-2-enedioic acid (1:1)

i) *N*-[3-(4-{[6-(Benzyl{(2*R*)-2-[4-(benzyloxy)-3-(formylamino)phenyl]-2-hydroxyethyl}amino)hexyl]oxy}but-1-ynyl)phenyl]-*N'*-pyridin-3-ylurea

Prepared using methods similar to those described in Example 1 i)

LCMS RT = 3.15 min.

ii) *N*-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]-*N'*-pyridin-3-ylurea

Prepared using methods similar to those described in Example 1 ii)

LCMS RT = 2.42 min, ES+ve *m/z* 564 $(MH)^+$

iii) *N*-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]-*N'*-pyridin-3-ylurea with (2*E*)-but-2-enedioic acid (1:1)

N-[3-(4-{[6-({(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)phenyl]-*N'*-pyridin-3-ylurea (74 mg) was dissolved in methanol (2 ml) and (2E)-but-2-enedioic acid (7.7 mg) was added. The solvent was removed under reduced pressure and the residue was triturated in diethyl ether to give the *title compound* (76 mg) LCMS RT= as above

Example 4

N-[3-(4-{[6-({2-hydroxy-2-[5-hydroxy-6-(hydroxymethyl)pyridin-2-yl]ethyl}amino)hexyl]oxy}butyl)-5-methylphenyl]urea formate

i) *N*-(3-Bromo-5-methylphenyl)urea

To a solution of 3-bromo-5-nitrotoluene (1500g) in glacial acetic acid (11 l) in a nitrogen purged hydrogenation vessel was added 5% platinum on carbon (approx 50% water wet paste) and the mixture was hydrogenated under 4 bar hydrogen pressure at room temperature. On completion of hydrogen uptake the catalyst was removed by filtration and the filtrate split into two equal portions. Each portion was set to stir separately and a solution of potassium cyanate (500g) in water (1.25 l) was added to each over 15 min. After stirring for an additional 15 min water (10 l) was added and the precipitated solid isolated by filtration and washed with water. The water wet cakes were combined and dissolved in hot EtOAc (3 l) and the aqueous phase separated. The organic phase was cooled with stirring to crystallise the product, which was isolated by filtration and washed with fresh EtOAc (2 l) and air dried overnight. Recrystallisation from EtOH (2.7 l) afforded the *title compound*. (565g) LC RT=3.9 mins.

ii) 6-Bromohexyl but-3-enyl ether

1,6-Dibromohexane (750g) was added to a stirred solution of sodium hydroxide (375g) in water (750ml). Tetrabutylammonium bromide (6.5g) was added and the two-phase mixture warmed to 50-55°. 3-Buten-1-ol (150g) was added over about 30 min and stirring continued at 50-55° for 4-6 h. The mixture was cooled, diluted with *tert*-butyl methyl ether and the layers separated. The organic layer was washed twice with water followed by brine and evaporated under vacuum to give the product as a liquid. This was purified by

silica column chromatography, eluting initially with hexane then with 2.5% EtOAc in hexane. Product fractions were combined and evaporated to give the *title compound* (237g). GC RT = 10.1 min.

iii) *N*-(3-{4-[(6-Bromohexyl)oxy]butyl}-5-methylphenyl)urea

6-Bromohexylbut-3-enyl ether (80g) was weighed into a nitrogen purged flask and a 0.5M solution of 9-BBN in THF (800ml) added with stirring over 1-2 minutes. The resulting solution was left to stir at room temperature for 3 h, then a solution of potassium phosphate (144g) in water (204ml) was added. N-(3-Bromo-5-methylphenyl)urea) (74g) was added followed immediately by palladium acetate (0.8g) and triphenylphosphine (1.8g). The mixture was heated to 60° and maintained at this temperature for 1-4 h until the reaction was complete. The mixture was cooled to room temperature and the layers separated. The organic layer was washed with water and brine and evaporated to give the *title compound* (196g) which was used directly at the next stage. LC RT 6.0 mins.

iv) *N*-(3-{4-[(6-{[2-hydroxy-2-(2-phenyl-4*H*-[1,3]dioxino[5,4-*b*]pyridin-6-yl)ethyl]amino}hexyl)oxy]butyl}-5-methylphenyl)urea

A solution of 2-amino-1-(2-phenyl-4*H*-[1,3]dioxino[5,4-*b*]pyridin-6-yl)ethanol (EP220054A2, 100mg), *N,N*-diisopropylethylamine (0.08ml) and *N*-(3-{4-[(6-bromohexyl)oxy]butyl}-5-methylphenyl)urea (118mg) in DMF (2ml) under nitrogen was heated to 50° for 23h. The mixture was cooled to 20° and the solvent was evaporated *in vacuo* to give the *title compound* (378.9mg). LCMS RT 2.85mins

v) *N*-[3-(4-{[6-({2-hydroxy-2-[5-hydroxy-6-(hydroxymethyl)pyridin-2-yl]ethyl}amino)hexyl]oxy}butyl)-5-methylphenyl]urea formate

A solution of *N*-(3-{4-[(6-{[2-hydroxy-2-(2-phenyl-4*H*-[1,3]dioxino[5,4-*b*]pyridin-6-yl)ethyl]amino}hexyl)oxy]butyl}-5-methylphenyl)urea (378.9mg) in acetic acid (3ml) and water (1.5ml) was heated to 70° for 1.5h. The mixture was cooled to 20° and the solvent was evaporated *in vacuo* to give a residue. This was purified by Mass Directed Auto Preparative HPLC to give the *title compound* (27mg). LCMS RT 2.33 min, ES+ve 489 (MH^+)

BIOLOGICAL ACTIVITY

In vitro measurements of compound potency and intrinsic activity at the human Beta 1, 2 and 3 receptors.

Method 1

The potencies of the compounds of Examples 1-3 were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal). At the human beta 2 adrenoreceptor, compounds of said examples had IC_{50} values below 1 μM.

Method 2

Potency of compounds of the invention at the human beta 2, 1 and 3 receptors was also determined using Chinese hamster ovary cells co-expressing the human receptor with a reporter gene. Studies were performed using either whole cells or membranes derived from those cells.

The three beta-receptors are coupled *via* the Gs G-protein to cause a stimulation of adenylate cyclase resulting in increased levels of cAMP in the cell. For direct cAMP measurements either membranes or cells have been used with either the HitHunter enzyme fragment complementation kit (DiscoveRx) or the FP^2 fluorescence polarisation kit (Perkin Elmer) to quantify the levels of cAMP present. These assays provide a measure of agonist potency and intrinsic activity of the compounds at the various receptors.

The reporter gene in the cells has also been used to quantify potency at the beta 1 and 3 receptors. This is a reporter of cAMP levels using the cAMP response element upstream of a firefly luciferase gene. After stimulation of the receptor with an agonist an increase in the level of luciferase is measured as a quantification of the level of cAMP in the cell.

In this assay the potency of compounds at the human beta-2 receptor is expressed as a pEC_{50} value. Compound of Example 4 had a pEC_{50} of >6.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims: